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A holistic evaluation of risks associated with the use of progestogen-based hormonal contraceptive among reproductive age women in Ilorin: Hematological and biochemical perspectives

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Abstract

Background: Despite the effectiveness of hormonal contraceptives (HCs) in birth control, many women remain hesitant to adopt it, while some are abandoning it due to concerns about potential side effects. These fears are often driven by conflicting reports in the existing literatures regarding the risks associated with their use, particularly concerning long-term health impacts on critical organs and systems. In view of this background, this study evaluated likely progestogen-based hormonal contraceptives (PHCs) associated risk among the inhabitants of Ilorin metropolis.

Methods: A total of 325 participants comprises of 220 PHC users and 105 non-users were recruited for the study, their socio-demographic were obtained using questionnaire. Comprehensive hematology and coagulatory parameters as well as various organ's specific biomarkers and anthropometric data were evaluated among the two groups using standard methods and procedures. Quantitative and qualitative variables were expressed in mean ± SD and percentage respectively. Student' test and descriptive analysis was used for the comparisons. Logistic regression was used to assess the independent effect of PHCs on coagulation factor alteration, controlling for potential confounders. SPSS version 26.1 was used for the statistical analysis, and $p<0.05$ was considered statistically significant.

Result: The outcome revealed higher frequency of abnormalities in both the rate and the duration of menstrual blood flow in PHC users than non-users. The result also showed that mean RBC count was significantly higher among PHCs users (p=0,010), while both aPTT and Protein-S were significantly reduced in the PHC users than that of non-users ($p = 0.002$) and ($p = 0.004$) respectively.

Conclusion: This finding concludes that both short and long-term usages of PHC is not associated with anemia, inflammation, renal, and cardiac. However, it's resulted in mild thrombotic and hepatic injury.

Keywords: Contraception; Progestogen; Hormonal contraceptives; Progestogen-based HC

1. Introduction

Hormonal contraceptives (HCs) are widely used by women of reproductive age as a reliable method of family planning and birth control [1]. Despite their effectiveness, many women remain hesitant to adopt HCs due to concerns about

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potential side effects [2]. These fears are often driven by conflicting reports in the existing literatures regarding the risks associated with their use, particularly concerning long-term health impacts on critical organs and systems. For instance, in respect to the level of red blood cell counts (RBC) among HCs users, elevated level was reported by [3]. On the contrary, both [4] and [5] reported lower RBC counts among HCs users. To compound the issue, [6] observed insignificant differences between the users and non-users. Aside from hematological abnormality, other common concerns among potential users include risks of renal, cardiac, hepatic injuries, as well as the possibility of inflammatory and thrombotic events.

Progestogen-based contraceptives (PHCs), as name imply consist of only progesterone analogue as the active ingredient, and exist in various forms [7]. Virtually all synthetic progesterone analogues, such as levonorgestrel and norethindrone, are synthesized from testosterone [8]. Factors that determine effectiveness of progestin-only contraceptives are; dosage, potency, and half-life of the progestin. More so, user-dependent factors, such as compliance to the prescription schedule can as well influences the efficiency of PHCs [9]. Based on their duration of action, PHCs can be categorized into short acting, intermediate acting, and long acting formulations. In respect to the concentration of progestogen, PHCs can be grouped into low dose, intermediate dose and high dose [10]. The low dose PHCs inconsistently inhibit ovulation in about 50% of cycles [11]. The intermediate dose allow some follicular development but much more consistently inhibit ovulation in roughly 97–99% of cycles [7]. While, high dose PHCs completely hinder follicular development and ovulation [12]. In addition to the above mechanism of the action, the three forms shared the ability to thicken the cervical mucus, thus reducing sperm viability and penetration [13].

This study provides a holistic evaluation of the likely associated risks with progestogen use among reproductive-age women in Ilorin. We conducted a comparative analysis of renal, cardiac, hepatic, inflammatory, anemic, and thrombotic risks between different forms of progestrogen users and non-users to provide a clearer understanding of the health implications of PHCs. By addressing these specific areas of concern, we aim to contribute to the ongoing debate surrounding HC safety and offer evidence-based guidance for women and healthcare professionals in the region.

2. Material and methods

2.1. Study area and design

A comparative cross-sectional study was conducted in Ilorin metropolis at four family planning clinics under Kwara State government. Ilorin is located on longitude 8.5373^{o}N and latitude 4.5444^{o} E, in north-central, Nigeria. The family planning clinic delivers services such as antenatal care, post-natal care, and contraceptive services. This study was conducted between March to September, 2024

2.2. Data collection

Questionnaire and direct interview was used to gather socio-demographic data such as age, gender, marital status, family type, history and duration of contraceptive usage. Anthropometric data were as well measured, while laboratory investigation also obtained for further analysis. Laboratory tests included hematological parameters, clotting profile, fibrinolytic profile, and their ratios, as well as renal, cardiac and hepatic related biomarkers.

2.3. Inclusion/ exclusion criteria

Every female from age 15 to 40 years with positive history of any form of PHCs (injectable, Implant, or vaginal rings) for at least six months prior to March, 2024. For the control group, women between the ages 15 to 40 years who visited the family planning clinic and have never taken any contraceptive in the last one year. Individual with pre-existing coagulation disorders or other major medical conditions affecting hemostasis were excluded from the study. Those below 15 or above 40 years of age, those who were unwilling to provide informed consent for study participation, lactating and pregnant women, individuals with history of chronic illnesses like diabetes mellitus, hypertension, kidney disease, cardiac disease, human immunodeficiency virus (HIV), hepatitis, or critically ill were as well excluded.

2.4. Operational definition

Hormonal contraceptive: woman using any form of progestogen (a progesterone analogue), in any of the form listed below;

- 2-months-injectible: any participant using an intramuscular or subcutaneous injectable contraceptive at 2 month interval for at least six months, it contains 150mg/ml of levonorgesrel and norethindrone.

- 3-months-injectible: any participant using an intramuscular or subcutaneous injectable contraceptive at 3 month interval for at least six months, it contains 150mg/ml of levonorgesrel and norethindrone.
- Implant: any participant having plastic rod impregnated with 68 mg of levonorgesrel and norethindrone placed under the skin of her upper arm for at least six months.
- Vaginal ring: any participant having non-biodegradable material impregnated with levonorgesrel and norethindrone habitually inserted inside her vagina.
- Non-user: any participants who did not use any form of PHCs in the last one year.

2.5. Statistical analysis

Statistical analysis was carried out using the IBM SPSS version 20 for window software (SPSS Inc. Chicago, IL USA). Descriptive analysis, and Student's test was used for the comparisons of data. Quantitative variables are presented as mean ± SEM and qualitative variables as percent. P-values < 0.05 were considered significant. Logistic regression was used to assess the independent effects of PHCs use on hematological and clotting profile alterations, controlling for potential confounding factors.

3. Results

3.1. Socio-demographic data

As shown in Table 1, a total of 220 reproductive-age women who were attending family planning clinics under the Kwara State government hospitals from March to September, 2024 were included in the study. Based on the form of HC adopted, more than half of the participant were 3-months injectable users (54%), implant users (30.5%), 2-months injectable users (10.5%) and vaginal ring users (5%). The mean age of the subjects was (28.0 ± 9.26) years. Of the participants, 196 (89.1%) were married and 129 (58.6%) were artisans and merchants. Regarding their educational status, 87 (36.3%) were attended college and above.

3.2. Comparison of the duration in days of menstrual flow between PHCs users and non-users

Figure 1 show the percentages of irregularities in the number of menstrual days. 37.7% and 12.4% were recorded in users and non-users respectively. Those who experienced reduced number of days were 33.6% and 9.5% respectively in the users and non-users. While 22.3% reported prolonged days of flow in the users, the incident was 7.6% among non-users. Notably, 70.5% of non-users had were predictable and regular number of days, whereas only 6.4% of PHC users reported such.

3.3. Comparison of the rate of menstrual flow between PHCs users and non-users

Figure 2 show the percentages of those with irregular menstrual blood flow. 29.1% was recorded in PHC users against 10.5% in non-users. While 21.4% reported normal volume of blood flow in PHC users, the percentage was 56.2% in non-users. The percentages of those who reported reduced and larger volume/blood flow among the PHC users were 41.4% and 8.2% respectively. Whereas, their percentages in non-users were19% and 14% respectively.

3.4. Comparison of hematology and coagulatory parameters between PHCs users and non-users

Table 2 shows the comparative analysis of hematology and coagulatory parameters between PHC users and non-users control. While significant elevation was observed in the mean level of RBC count, reduction were observed in concentration of Protein-S, with reduced aPTT duration in HCs users in relation to non-users. However, no significant differences were observed in the level of the remaining parameters between the two groups.

3.5. Comparison of biochemical parameters between PHCs users and non-users

Table 3 shows the comparison of concentration of biochemical analytes between PHC users and non-users control. While ALT activity was higher in PHC users, LDL was reduced, though, no significant differences were observed in the level of the entire parameters between the two groups.

3.6. Logistic regression analysis

The mean ± SD value for the D-dimer to platelet ratio (DPR) was higher in PHCs users with reduced aPTT time than those with normal aPTT (34.2±37.6) vs. (16.2±25.5). In the univariate analyses, the duration of PHC's uses, D-dimer, platelet count, Protein-S and PT values showed statistically significant associations with hypo-coagulable state. After adjusting for these variables, only protein-S showed an association with reduced aPTT.

Table 1 Demographic characteristics and drug history of studied participants

Characteristics	PHCs users	None-PHCs users
Number (Percentages)	220 (100%)	105 (100%)
Mean age (years)	28.0 ± 9.26	29.1 ± 8.69
Age range (years) 15 – 25	38 (17.3)	34 (32.4)
26 – 40	182 (82.7)	71 (67.6)
BMI (kg/m^2) Normal	183 (83.2)	82 (78.1)
Overweigh	37 (16.8)	23 (21.9)
Marital status Married	196 (89.1)	94 (89.5)
Single	24 (10.9)	11 (10.5)
Duration of HCs usage < 1 year	77 (35)	NA
1 – 5 years	81 (36.8)	NA
5 -10 years	62 (28.2)	NA
Forms of HCs adopted Implant	67 (30.5)	NA
Vaginal ring	11 (5.0)	NA
2-months-Inj	23 (10.5)	NA
3-months-Inj	119 (54.0)	NA
Occupation Student	17 (7.7)	8 (7.6)
Civil servant	56 (25.5)	30 (28.6)
Artisan/ merchant	129 (58.6)	53 (50.5)
House wife	18 (8.2)	14 (13.3)

Values are presented as mean ± standard deviation or number (%), HCs = hormonal contraceptives, BMI = body mass index, NA = not applicable.

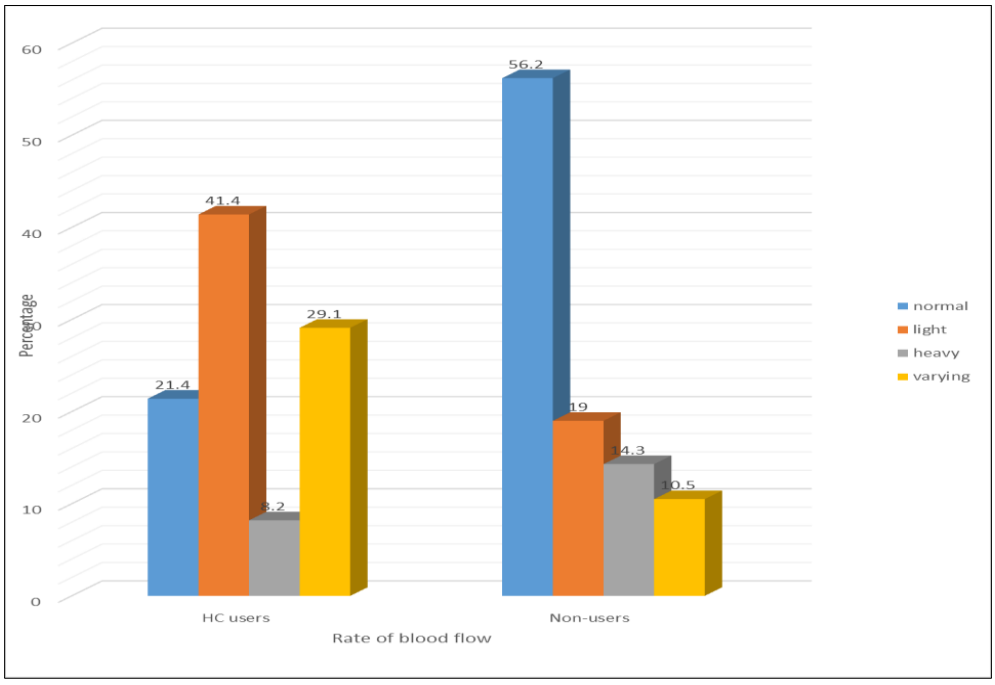

Figure 1 Bar chart comparing the rate of flow of menstrual blood between PHC's users and non-users in Ilorin

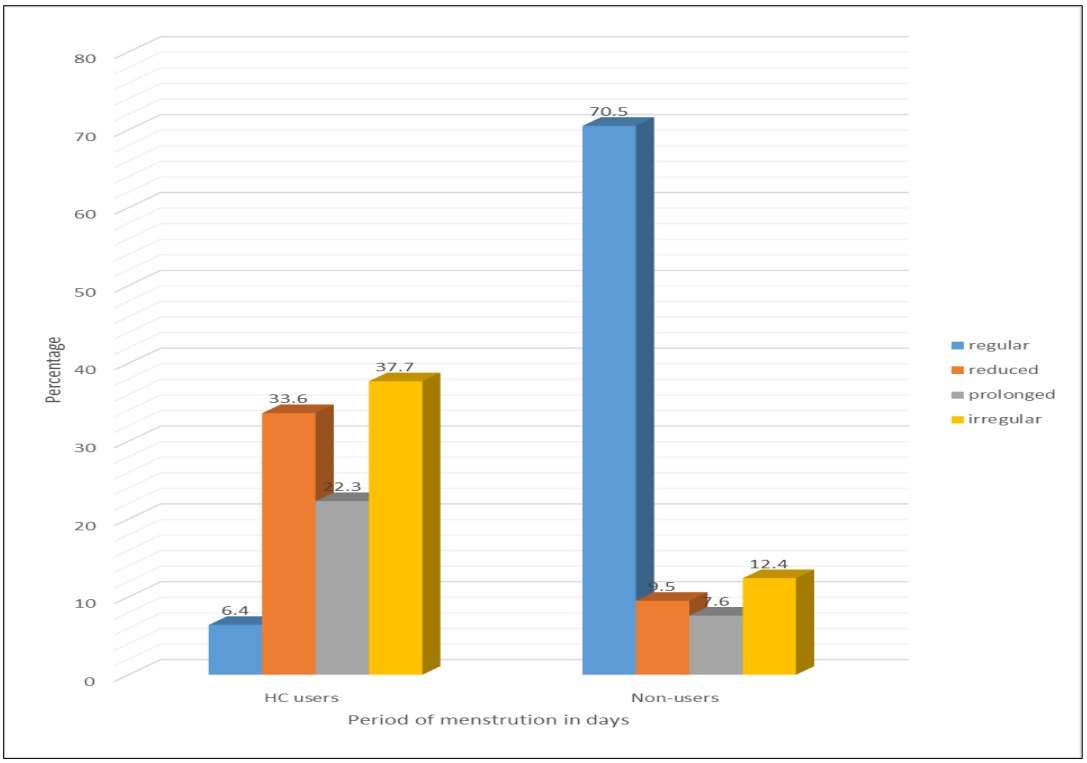

Figure 2 Bar chart comparing the period of flow of menstrual blood between PHC's users and non-users in Ilorin

Table 2 Comparison of hematological and coagulatory parameters between hormonal contraceptives users and non-users control

Parameters	PHCs users	Non-PHCs users	P-value
WBC counts (x 10^9/L)	5.14 ± 1.44	5.52 ± 1.62	0.386
Lymphocytes (%)	48.7 ± 9.05	47.8 ± 7.59	0.664
Granulocytes (%)	41.3 ± 9.85	41.8 ± 8.34	0.830
MID (%)	9.99 ± 3.16	10.41 ± 2.78	0.556
RBC counts (x 10^{12}/L)	4.30 ± 0.41	3.98 ± 0.43	0.010*
Hemoglobin (g/dL)	12.3 ± 1.09	11.9 ± 0.94	0.144
Hematocrit (%)	36.98 ± 3.44	34.98 ± 3.64	0.169
MCV (fL)	86.2 ± 6.64	88.3 ± 7.49	0.276
MCH (Pg)	24.29 ± 2.23	25.12 ± 2.33	0.190
MHCH (g/dL)	28.17 ± 1.06	28.44 ± 0.97	0.314
RDW-CV	15.25 ± 1.15	14.93 ± 0.83	0.209
RDW-SD	44.80 ± 3.23	45.14 ± 3.19	0.609
Platelet counts (x 10^9/L)	226.13 ± 55.49	207.11 ± 98.07	0.269
MPV (fL)	7.76 ± 0.89	9.79 ± 0.76	0.097
PDW (%)	11.38 ± 1.83	11.77 ± 1.73	0.387
PCT (%)	0.22 ± 0.49	0.22 ± 0.81	0.962

P-LCR (%)	25.37 ± 6.56	25.62 ± 5.89	0.876
PLCC	55.53 ± 14.04	54.44 ± 16.34	0.800
Fibrinogen (g/L)	2.64 ± 1.33	2.74 ± 1.96	0.747
D-Dimer (g/dL)	491.09 ± 373.1	438.68 ± 376.1	0.094
Protein S (fL)	18.77 ± 2.57	24.33 ± 1.56	0.002*
Prothrombin Time (sec)	12.79 ± 4.31	14.94 ± 2.11	0.256
aPTT (sec)	25.18 ± 3.75	33.83 ± 8.78	0.004*

The values are mean ± standard deviation, Student t-test was used to compare the means at p = 0.005, RDW = red cell distribution width, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MPV = mean platelet volume, P-LCR = platelet-large cell ratio, PCT = plateletcrit, aPTT = activated partial thromboplastin time.

Table 3 Evaluation of other risks between HCs users and non-HCs users

Characteristics	**PHCs users**	**Non-PHCs users**	**p-value**
WHR	0.95 ± 0.25	0.97 ± 0.90	0.268
BMI (Kg/m^2)	23.20 ± 2.75	22.01 ± 4.37	0.165
Total cholesterol (mmol/L)	3.40 ± 0.47	4.55 ± 0.78	0.262
Triglyceride (mmol/L)	1.03 ± 0.15	1.10 ± 0.14	0.659
LDL (mmol/L)	2.13 ± 0.25	3.65 ± 0.64	0.059
TC/HDL	4.43 ± 0.19	7.43 ± 2.49	0.052
Troponin I (ng/mL)	0.21 ± 0.04	0.19 ± 0.07	0.974
sNGAL (ng/mL)	89.7 ± 11.4	91.1 ± 18.6	0.659
Creatinine (µmol/L)	63.67 ± 8.57	64.5 ± 3.87	0.891
Urea (mmol/L)	3.04 ± 1.43	4.25 ± 0.19	0.662
eGFR (mL/min/1.73)	125.67 ± 16.3	128.00 ± 7.1	0.841
UCR	0.032 ± 0.01	0.035 ± 0.09	0.823
Phosphate (mmol/L)	0.91 ± 0.43	1.03 ± 0.34	0.783
Albumin (g/L)	42.00 ± 3.64	41.54 ± 2.12	0.832
ALT (IU/mL)	9.6 ± 5.21	5.3 ± 1.39	0.117
hsCRP (µg/L)	3.06 ± 1.64	3.16 ± 0.38	0.962
CAR	0.07 ± 0.04	0.07 ± 0.03	0.951
DFR	124.39 ± 28.5	158.86 ± 32.7	0.605
DPR	0.90 ± 0.38	1.09 ± 0.65	0.007*
PLR	4.85 ± 1.68	4.96 ± 2.35	0.104
GLR	0.92 ± 0.40	0.93 ± 0.35	0.513

The values are mean ± standard deviation, Student t-test was used to compare the means and p = 0.005, BMI = Body mass index, WHP = Waist to hip ratio, sNGAL = serum neutrophil gelatinase-associated lipocalin, UCR = Urea to Creatinine ratio, ALT = Alanine aminotransferase, HsCRP = high sensitive C-reactive protein, CAR = HsCRP to Albumin ratio, DFR = D-dimer to fibrinogen ratio, DPR = D-dimer to platelet ratio, PLR = Platelet to lymphocytes ratio, GLR = Granulocytes to lymphocytes ratio.

Table 4 Odd ratios for aPTT abnormality according to as DPR a continuous variable

	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age (year)	0.964	0.945 – 1.023	0.523	-	-	--
BMI (Kg/m^2)	0.552	0.233 – 1.306	0.176	-	-	--
HCs form	0.562	0.243 – 1.307	0.187	-	-	--
Duration	0.364	0.144 – 0.921	0.033*	0.564	0.386 – 1.106	0.109
D-dimer	0.388	0.274 – 0.748	0.001*	-	-	--
Fibrinogen	1.477	0.587 – 3.768	0.452	-	-	--
Protein-S	3.873	2.648 -7.310	0.009*	2.538	1.873 – 5.834	0.042*
PT (sec)	0.864	0.787 – 0.949	0.009*	0.972	0.866 – 1.091	0.630
PLT	0.332	0.142 – 0.864	0.004*	-	-	--
Hemoglobin	0.894	0.865 – 1.123	0.904	-	-	--
RBC count	0.897	0.795 – 1.087	0.867	-	-	--
DFR	1.365	0.786 – 2.654	0.254	-	-	--

D = Duration of PHCs uses, PT = Prothrombin time, PLT = Platelet, DFR = D-dimer to fibrinogen ratio, DPR = D-dimer to platelet ratio, PLR = Platelet to lymphocytes ratio,

4. Discussion

Ilorin, a rapidly growing city in Nigeria, mirrors global patterns of HC use, with many women avoiding or discontinuing these contraceptives due to perceived health risks. Though, considerable number of the inhabitants' practices one form of the natural method contraceptive or the other [2]. The lack of consensus in the scientific community on the magnitude and nature of these risks further compounds the uncertainty, leaving women and healthcare providers alike uncertain about the safety of prolonged HC use [13]. Our preliminary finding among the inhabitants of Ilorin revealed majority of non-users exhibits exaggerated fear against HCs generally. We aimed to identify association between PHCs uses and different health risks. This is the First population-based study to evaluate comprehensive hematological and biochemical parameters in this part of world.

A total of 220 reproductive age women using various forms of PHCs were recruited, along with 105 age-matched non-user control (Table 1). Comprehensive hematological and biochemical parameters were analyzed as an inexpensive and easily accessible tools for PHCs safety evaluation. Multiple biomarkers can improve sensitivity and specificity of diagnostic test [14]. Both multiple and single parameters was adopted in the evaluation of the following risks; obesity, anemia, thromboembolism, systemic inflammation, cardiovascular injury, renal injury and hepatic function among others.

A quota consecutive method was adopted, given the large sample size requirements and strict exclusion criteria. Though a non-probability method, but allows easier sample selection and is advantageous when dealing with large sample sizes, as it enables working with multiple samples at lower relative cost and time compared to probability sampling methods [15].

4.1. The evaluation common menstrual abnormality

The current study evaluated menstrual irregularities such as variations in the number of days of blood flow, and the rate of flow among PHC users in relation to non-users.

As presented in Figure 1, irregularities in the number of menstrual days were significantly higher among PHC users than non-users. Specifically, 37.7% of PHC users reported unpredictable number of their days since they started using contraceptives, compared to 12.4% reported among non-users. The figure also revealed that 33.6% and 22.3% reported reduced and prolonged number of menstrual days respectively among the PHC users. Whereas, the corresponding percentages among non-users were 9.5% and 7.9%. Notably, 70.5% of non-users reported predictable and regular

number of days, whereas only 6.4% of PHC's users reported normal duration of flowing PHC use. These findings align with previous studies by [16] and [17].

Figure 2 revealed patterns of responses from the participants in relation to the rate of their menstrual flow in the last six months and from the inception of PHC uses. 21.4% reported having a normal flow among PHC users, in contrast the percentage was 56.2% in non-users. The percentages of those with light, heavy and inconsistent rate of flow were 41.4%, 8.2% and 29.1% respectively among the users. The corresponding percentages in non-users were 19%, 14.3% and 10.5% respectively. The higher incidence of reduced blood flow among PHC users, as observed in this study, may be considered a positive outcome. Because anemia is a common consequence of prolonged and heavy bleeding, with significant adverse effects on health and economic well-being [18]. Overall, these findings indicate that PHC use may influence menstrual patterns, highlighting the need for further investigation into the implications of these changes on women's health. On the other hand, our data also revealed that apart from PHC, other unidentified factors might responsible menstrual irregularities as data from non-PHC user's shows. More so, rather than generalizing it that it increases menstrual bleeding, the extent or percentage is more appropriate.

4.2. Obesity and metabolic disorder assessment

Both BMI and WHR were used for the evaluation of obesity and metabolic risk in our study. BMI is one of the widely used parameter for classifying individuals based on weight relative to height [19]. On the other hand, the WHR is an indicator of fat distribution, with higher ratios often associated with central (or visceral) obesity, which carries a greater risk for metabolic diseases [20].

As revealed in table 2, the absence of significant differences in BMI and WHR in this study supports the notion that PHC use does not necessarily lead to weight gain or obesity. Many studies have shown similar findings; [21] conducted a systematic review and found that most users of modern HCs do not experience significant weight gain, particularly those using combined oral contraceptives (COCs). Also, [22] showed that WHR remains stable among PHC users, particularly for those on low-dose PHCs, which have been shown to have minimal effect on abdominal fat distribution. Moreover, [23] concluded that initial increases in weight for some HC users are often temporary or are within the range of natural weight fluctuations. Thus, this finding are reassuring, suggesting that PHC use does not contribute to central obesity or lead to weight gain in a way that would increase metabolic risk.

4.3. Anemia risk

Anemia was defined as HBG level <11g/dl for both males and females based on the WHO cutoff value. Reduced level of hemoglobin is associated with reduced oxygen-carrying capacity [24]. On the other hand, hematocrit, is one the vital parameters for evaluating anemia, and it is the proportion of blood volume occupied by RBCs [25]. Three hematological parameters were reviewed between the PHC's users and non-users, namely hematocrit, hemoglobin level and RBC count.

A moderately higher but insignificant level of HBG and hematocrit were recorded in PHC users in relation to non-users (Table, 2). The lack of significant differences in both parameters further supports the finding that not all HC uses lead to an increased risk of anemia [26]. This could be attributed to lighten of menstrual bleeding, which helps conserve iron and prevents anemia. In fact, some studies have found that COCs, may even help to stabilize or increase Hb levels due to reduced menstrual blood loss [27, 28].

The RBC count is another important marker of anemia, with low counts indicating potential deficiencies in RBC production or increased its loss [29]. The significant elevation in RBC counts observed in PHC's users in this study ($p = 0.010$), suggest that PHC does not compromise RBC production, it rather enhances erythropoiesis or inhibit the rate of hemolysis. This aligns with findings by [26], which showed that COC users had stable or slightly higher RBC counts compared to non-users. These effects could be attributed to the influence estrogen, which may prevent excessive blood loss and help maintain stable RBC levels [28].

4.4. Thromboembolic risk assessment

There was no homogeneity in the pattern of thrombotic parameters evaluated in this study. While there were no significant differences in the values of parameters such as; fibrinogen, D-dimer, DFR, PLR and PT between the PHC users and non-users, the differences in aPTT, Protein-S and DPR were significant (Table 2 and 3). The unchanged fibrinogen, D-dimer, DFR, PLR and PT values align with previous findings such by [29], suggesting coagulatory biomarkers often shown variable responses to HCs depending on the specific type and dosage of hormones used. In fact, D-dimer levels is more directly influenced by active clot formation and breakdown and may not necessarily increase with HC use [30].

The stability in these parameters could indicate that, for many women, modern PHCs may not cause substantial changes in baseline coagulation markers that are typically associated with thromboembolic risk. These finding revealed that all coagulation markers are not equally affected by PHC use.

Nonetheless, the observed significant decrease in aPTT ($p = 0.004$), Protein S ($p = 0.02$), and DPR ($p = 0.007$) in PHC users is noteworthy and indicates potential changes in the coagulation pathway that could predispose PHC users to thromboembolic events. A shortened aPTT suggests a faster intrinsic pathway coagulation, which could indicate a hyper-coagulable state [31]. Also, reduced levels of Protein S, an anticoagulant protein, are particularly significant because it plays a crucial role in inhibiting clot formation by enhancing the anticoagulant effects of Protein C [32]. A range of studies supports the notion that HCs, especially those containing estrogen, can influence coagulation markers such as Protein S and aPTT, thereby contributing to an increased risk of thromboembolism [33, 34, 35]. The DPR is a valuable predictor of pulmonary embolism, which enhance the specificity of D-dimer and improve its accuracy [36]. The significant lower DPR in PHC's users reflects the imbalance between clot formation and platelet activity that favors thrombosis. While studies evaluating DPR in HC users are limited. It has been confirmed that altered protein-S and aPTT potentiate thrombotic risk, particularly in women with additional risk factors [37].

4.5. Assessment of systemic inflammation

Inflammation is an integrated immune response and a key defensive apparatus against the disturbance of homeostasis in infectious and injurious conditions [38]. Studies have shown that inflammation plays an important role in several disease conditions such as atherosclerosis, acute kidney injury and cardiovascular disease among others [39]. The parameters adopted for evaluating systemic inflammation in this study are; hsCRP, Albumin, CAR, NLR and fibrinogen; [40]. NLR reflects the balance between neutrophils and lymphocytes and is commonly used as a biomarker for cardiovascular and inflammatory conditions [41]. The CAR is a highly specific marker of low-grade inflammation and is often elevated in cases of cardiovascular risk or systemic inflammation [42].

As revealed in Table 3 and 4, there were absence of significant differences in the entire above mentioned parameters between the HC users and non-users. Our finding on NLR was aligned with [43], while report on Albumin was in consonant with that of [44]. There is paucity of information on impact of HC uses on CAR in the available literatures. Though, finding by [45] NL, noted that certain COC may mildly elevate hsCRP levels. Nonetheless these changes are often small and not necessarily indicative of a clinically significant inflammatory response. These findings suggest that PHCs, especially modern low-dose formulations, do not trigger inflammatory responses sufficient to alter the plasma level of those parameters. This stability may be due to advancements in PHC formulations, which now often include lower doses of estrogen, known to reduce the risk of systemic inflammatory effects [46]. Fibrinogen also serves as an inflammatory biomarker that increase in response to inflammation or tissue damage [47]. In this study, fibrinogen levels were similar between PHC users and non-users, which aligns with findings of [48]. Thus, suggesting that PHC use alone may not elevate inflammatory biomarkers or promote systemic inflammation without underline cardiovascular risk factors.

4.6. Cardiovascular injury and diseases assessment

Cardiovascular disease (CVD) is one the major global health challenge and the leading cause of death worldwide [49]. In order to evaluate cardiovascular risk in our study, lipid profile and anthropometric data were compared between the HC users and non-users. Lipid profile offers supplementary insights in evaluating the risk of CVD, and epidemiology study has revealed association between the profile and CVD and death [50].

Our observation of lack of significant differences in BMI, WHR, TG, and TC between HC users and non-users aligns with that of [51] and suggesting that PHCs do not consistently influence these parameters substantially. Though, [52] reported that some estrogen-progestin containing HC may slightly elevate TG due to the estrogen component; though, this effect is generally mild and varies by HC formulation and individual response [13]. Furthermore, the same author observed a modest improvement in both high- and low-density lipoproteins (HDL and LDL) levels respectively. Interestingly, we observed moderately lower LDL and TC/HDL ratio values among HC users in this study. The finding is in line with that of [53] and [54] that HC may lead to an increase in HDL, while keeping LDL relatively stable, depending on the dosage and specific formulation, thus mitigating the risk factors associated with lipid profiles. An elevation in LDL level and TC/HDL ratio are strongly associated with risk of atherosclerosis and CVD due to their role in promoting plaque formation in the arteries [55]. The TC/HDL ratio is particularly predictive of CV outcomes, as it reflects the balance between atherogenic and protective lipoproteins [56]. For the BMI and WHR, previous research has indicated that HC use does not necessarily result in weight gain or increased BMI [57], as commonly perceived; any changes tend to be minimal or vary depending on the individual and the specific type of contraceptive used.

Myocardial injury was evaluated in this study by comparing random serum cardiac Troponin I (cTnI) level in both PHC users and non-users. cTnI is a myocardium-specific protein that is part of constitutive myocardial function [58]. An elevation in the value of cTnI above two times the upper limit of normal is considered a sensitive and specific diagnostic test for myocardial injury [59]. As revealed on the Table 3, lack of significant difference in serum level of cTnI between the two studied groups indicated that PHC uses did not associate with neither substantial none ongoing myocardial necrosis.

4.7. Hepatotoxicity and hepatic function assessment

Hepatotoxicity was assessed in our study using ALT, while hepatic functions was evaluated using Albumin, fibrinogen and PT. The liver is the predominant source of ALT, thus a rise in its plasma activities is a sensitive indicator of damage to hepatocytes cytoplasmic and/or mitochondrial membranes [60]. A mild insignificant elevation was noted in ALT activity in PHC users. This finding is in consonant with [61] However, [62, 63 and 64] reported a significant elevation in ALT in PHC users. The likely mechanism of hepatotoxicity could either be related to depletion of cytochrome P-450 [65], or via enhancement oxidative stress [66]. The discrepancy in ALT result could be related to the nature of HCs or genetic predisposition and other unidentified factors.

The hepatic function was measured by Albumin, fibrinogen and prothrombin time. Both Albumin and fibrinogen are predominately synthesized in the liver, so both serves as sensitive markers of hepatic function and protein synthesis capability [67]. The absence of significant differences in their levels in the two study groups suggests that HC use does not impair hepatic protein synthesis. [68], [64] had earlier reported similar finding. Although some older studies suggested that HCs with high estrogen doses could mildly elevate fibrinogen levels, more recent studies on low-dose contraceptives have shown that they typically do not cause significant increases in fibrinogen [69, 70]. Prothrombin time is a critical parameter in assessing liver function, because liver produces many clotting factors [71]. The lack of significant differences in PT between PHC users and non-users suggests that PHCs do not adversely impact the liver's ability to produce coagulation factors.

4.8. Renal function and injury assessment

While both tubular function and renal injury were evaluated with single parameters, multiple parameters were adopted for the GFR evaluation in this study. This finding is supported by [72], and further support the safety of PHCs concerning liver-related coagulation function.

For the basic evaluation of tubular function, serum phosphate concentration was compared between the two groups. Tubular reabsorption of phosphate (TRP) has been identified as a simple and reliable surrogate marker fort mild to moderate renal insufficiency assessment [73]. The absence of significant difference in serum phosphate levels between HC users and non-users in this study suggests that PHC use does not impair renal tubular function. There is paucity of information in the available journals on the impact of PHC on tubular function using TRP.

Serum creatinine, urea and eGFR were adopted for the evaluation glomerular filtration rate (GFR). The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used for the eGFR estimation, because it is currently considered to be the best for evaluating renal function [74]. Both urea and creatinine are reliable markers of renal function, with creatinine in particular serving as a direct indicator of glomerular filtration efficiency [75] eGFR is a primary and sensitive marker for the assessment of kidney function filtration capacity [76]

The lack of significant differences in urea, creatinine, and eGFR between PHC users and non-users indicates that renal filtration capacity remains unaffected for most users. Furthermore, any changes in these biomarkers tend to be transient and return to baseline once HC use is discontinued. Our finding was in line with [77, 78]. A stable UCR also reflects a balance in protein metabolism and renal function, suggesting that the use of HCs does not impair these metabolic processes [79].

Serum neutrophil gelatinase-associated lipocalin (sNGAL) is a sensitive indicator of tubular stress or injury and is often elevated in cases of acute kidney injury or chronic kidney disease. The lack of significant difference in sNGAL levels between PHC users and non-users suggests that HC use does not predispose users to renal injury. [80, 81], also found that sNGAL levels remained stable in PHC users, further supporting the findings that PHCs do not exacerbate renal stress or lead to kidney injury.

Generally, the discrepancies observed in few of our results and that of previous studies could be attributed to either different in sample size, genetic variation among of subjects, the formulation of hormonal contraceptives, or analytical

methods used. Furthermore, some of the studies offered had flaws such as a lack of appropriate comparison groups or were too small to draw meaningful conclusions.

5. Conclusion

In this study, we conducted a comprehensive evaluation of the health risks associated with the use of HCs among reproductive-age women in Ilorin. Our findings aligned with a growing body of literature suggesting that modern low-dose PHCs does not significantly predisposed to obesity, metabolic syndrome, systemic inflammation, hepatic synthetic dysfunction, myocardial injury, cardiovascular diseases, renal tubular and glomerular functions dysfunction in healthy women.

Interestingly, PHC uses was found to be associated with a slight cardio-protective benefit and anemia-preventive characteristics. These findings offer reassurance regarding the cardiovascular and hematologic safety of PHCs and highlight their potential benefits in managing the cases.

However, with respect to the thromboembolic risk, while some markers were unaffected by PHC use, the significant reductions in aPTT, Protein S, and DPR underscore potential risks associated with a pro-coagulatory state.

Conclusively, the detection of thrombotic and mild hepatic damage tendency highlights the need for ongoing monitoring and awareness of these potential side effects in PHCs users. Healthcare providers should take these risks into consideration when counseling patients, particularly those with pre-existing conditions that may exacerbate these effects. Despite the observed risks, the benefits of PHC use as an effective contraceptive method remain substantial, and with appropriate screening and monitoring, many women can safely use these contraceptives.

Recommendation and further study

Future studies could expand on these findings by examining how different types and doses of PHCs influence coagulation dynamics over longer periods. This may provide reassurance to women concerned about the associated risks with contraceptive use and highlights the need for further research into individualized responses to PHCs.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be understood as a potential conflict of interest.

Author's contribution

Oyeleke O.K.: Conceptualization, editing and validation
Fatima B. S.: Hematological analysis, writing original manuscript
Borisade M. S.: Provision of reagent and statistical analysis.
Lateefat R. A.: Clottology analysis, writing of manuscript.
Ben-Anefo T. C.: Provision of reagent, editing of final manuscript.
Ibrahim.E.S: Data curation, biochemical and statistical analysis.

Statement of ethical approval

Ethical approval for this study was obtained from the Ethical Review Committee, Kwara State Ministry of Health, Ilorin with the approval number; ERC/MOH/2024/03/191. The research was carried out in line with the ethics governing the use of human samples and in accordance with Helsinki declaration. Ethical practices such as participant consent, confidentiality and safety laboratory practice was observed during the study.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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